General

Guideline Title

Management of hepatitis C. A national clinical guideline.

Bibliographic Source(s)

Scottish Intercollegiate Guidelines Network (SIGN). Management of hepatitis C. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2013 Jul. 57 p. (SIGN publication; no. 133). [232 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Scottish Intercollegiate Guidelines Network (SIGN). Management of hepatitis C. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2006 Dec. 49 p. (SIGN publication; no. 92).

Any amendments to the guideline in the interim period will be noted on Scottish Intercollegiate Guidelines Network (SIGN) Web site .

Recommendations

Major Recommendations

Note from the Scottish Intercollegiate Guidelines Network (SIGN) and National Guideline Clearinghouse (NGC): In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the full-text guideline document.

The levels of evidence (1++, 1+, 1-, 2++, 2+, 2-, 3, 4) and grades of recommendations (A–D) are defined at the end of the "Major Recommendations" field.

Testing

Clinical and Cost-Effective Testing for Hepatitis C Virus (HCV)

D - The following groups should be tested for HCV:

- Blood/tissue donors
- Patients on haemodialysis
- Healthcare professionals who intend to pursue a career in a specialty that requires them to perform exposure prone procedures

D - The following groups should be offered an HCV test:

- Patients with an otherwise unexplained persistently elevated alanine aminotransferase
- People with a history of injecting drug use
- People who are human immunodeficiency virus (HIV) positive
- Recipients of blood clotting factor concentrates prior to 1987
- Recipients of blood and blood components before September 1991 and organ/tissue transplants in the UK before 1992
- Children whose mother is known to be infected with HCV
- Healthcare professionals following percutaneous or mucous membrane exposure to blood which is, or is suspected to be, infected with HCV
- People who have received medical or dental treatment in countries where HCV is common and infection control may be poor
- People who have had tattoos or body piercing in circumstances where infection control procedure is, or is suspected to be, suboptimal
- People who have had a sexual partner or household contact who is HCV infected

D - Dried blood spot testing should be considered as a convenient and cost-effective method of accessing some target populations.

D - There should be consideration given to methods to raise awareness and highlight information regarding hepatitis C amongst at-risk groups and the general public. The targeting of awareness campaigns to particular audiences is recommended. Staff should have access to appropriate training.

D - Anyone who has a negative test but remains at risk of infection should be offered further testing on an annual basis.

D - Testing for HCV should be offered to migrants from countries with a medium or high prevalence of HCV.

HCV Diagnostic Testing

Principles of Testing

B - Diagnostic testing for HCV should be performed on serum or plasma where possible.

D - HCV genotyping should be undertaken if antiviral therapy is being considered.

D - Following an isolated acute percutaneous exposure to blood infected, or strongly suspected of being infected, with HCV, healthcare professionals should be offered HCV ribonucleic acid (RNA) testing at six, 12 and 24 weeks and anti-HCV testing at 12 and 24 weeks.

Prevention of Secondary Transmission

Transmission Through Sexual and Household Contact

D - Individuals co-infected with HIV/HCV should be advised always to practice safe sex and use condoms.

D - Individuals infected with HCV should be advised to avoid activities which could result in percutaneous or mucous membrane exposure to their infected blood, such as the sharing of razors and toothbrushes.

Transmission Through Injecting Drug Use

D - Injecting drug users known to be infected with HCV should be given advice on how they can prevent transmission of infection to other injecting drug users.

Transmission Between Healthcare Professionals and Patients

Risk of Patient Infection

D - Healthcare professionals who are aware they are HCV RNA positive should not undertake exposure-prone procedures.

Referral

D - Individuals, including injecting drug users, diagnosed with chronic HCV should be offered integrated multidisciplinary care as it can maximise their uptake of, and retention in, services.

A - Patients with acute HCV infection should be referred to specialist care immediately.

Children and Hepatitis C

Mother to Child Transmission

B - In pregnant women knowledge of HCV RNA positive status should not influence obstetric management or standard advice regarding breast feeding.

HCV Testing in Children and Infants

B - Infants born to women who are HCV antibody positive and HCV RNA negative do not need to be tested.

B - In children born to women infected with HCV, an HCV antibody test should be performed at 12 months of age or older to identify the minority of children who are infected.

B - In children whose mothers are co-infected with HIV, and in infants found to be HCV antibody positive after 12 months, an HCV RNA test should be performed, and if positive, confirmed on a second sample.

B - If information regarding the risk of HCV infection in an individual child is required before 12 months of age, an HCV RNA test and retest can be performed after two months of age. Further testing is still required to make a definitive diagnosis.

Natural History of HCV Infection in Children

D - Children infected with HCV should be monitored to identify the minority who are at risk of progressive fibrosis during childhood, and who may be candidates for treatment.

Treatment of Children with Hepatitis C

A - Children infected with all genotypes of hepatitis C with evidence of moderate or severe liver disease should be considered for treatment with pegylated interferon (IFN) and ribavirin.

B - Children infected with HCV genotypes 2 and 3 should be considered for treatment with pegylated INF and ribavirin irrespective of disease stage.

C - In children with mild disease and infection with other genotypes, benefits of treatment need to be balanced against risks of side effects.

Acute Hepatitis C

Natural History

D - Patients with acute HCV infection require clinical and laboratory monitoring (looking for spontaneous viral clearance) for the initial three months following diagnosis as they will often have a self limiting illness.

Treatment of Patients with Acute Hepatitis C

Timing of Treatment

D - Treatment should start between three and six months after diagnosis of acute hepatitis C, if the infection has not resolved spontaneously.

Choice and Duration of Treatment

A - Patients with acute HCV infection should be treated with IFN therapy if the infection does not resolve spontaneously.

D - Patients can be treated with either pegylated IFN or non-pegylated IFN.

D - Patients with acute HCV infection should be treated with IFN therapy for 24 weeks irrespective of genotype.

Assessment of Liver Disease

Fibrosis Markers

B - Biochemical markers should not be used as an alternative to liver biopsy for staging of intermediate grades of fibrosis.

B - Biochemical tests may be used as an alternative to liver biopsy to diagnose cirrhosis or to direct screening for complications of fibrosis.

Liver Biopsy

When to Biopsy

D - Liver biopsy should be performed if there is concern about additional causes of liver disease.

D - Repeat liver biopsies should be considered in patients with mild disease who remain untreated, if progression of liver fibrosis would influence the decision to opt for antiviral therapy.

Biopsy and Genotype

D - Liver biopsy should not be considered an essential test prior to using antiviral therapy, especially in patients with genotype 2 and 3 disease.

Progression of Untreated Disease

Age, Gender and Ethnicity

D - When estimating the likely rate of progression of liver disease age at infection, gender and ethnicity should be considered.

Tobacco Smoking

D - Patients with chronic hepatitis C (CHC) should be advised that smoking tobacco can accelerate progression of liver disease.

Alcohol

B - Patients with CHC should be advised that drinking alcohol (even in moderation) can accelerate progression of liver disease.

Alanine Aminotransferase (ALT)

D - When defining persistently normal serum alanine aminotransferase (PNALT) serum ALT measurement should be undertaken every two to three months to ensure that flares in ALT are not missed.

HIV Co-Infection

B - The increased rate of progression to decompensated liver disease in patients with HCV and HIV co-infection should prompt early consideration of antiviral therapy.

Co-Infection with Hepatitis A or B Viruses

D - Vaccination against hepatitis A and B should be considered for patients infected with hepatitis C.

D - When estimating the likely rate of progression of liver disease as a result of hepatitis C infection, active or previous hepatitis B virus infection should be considered.

Iron Status

D - Modest iron loading does not justify specific intervention prior to antiviral therapy as it is unlikely to be of clinical importance.

D - Patients with significant iron retention require further investigation for additional conditions known to result in iron overload.

Treatment of Chronic Hepatitis C

Antiviral Therapy

A - All patients with chronic HCV infection should be considered for antiviral therapy.

Sustained Viral Response

B - Sustained viral response should be used as a marker for viral clearance.

Treatment Variation by Genotype

Genotype 1 and Duration of Treatment

A - All treatment-naive patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy.

A - All treatment-experienced patients infected with HCV genotype 1 should be considered for treatment with pegylated IFN and weight-based ribavirin with the addition of a protease inhibitor as triple therapy.

A - Response-guided therapy can only be used in treatment-naive patients and previous treatment relapsers who are not cirrhotic.

Genotype 1 and Duration of Treatment for Patients Unsuitable for Protease Inhibitors

A -

- Patients with genotype 1 infection should be tested for an early viral response (EVR) at 12 weeks.
- Patients with genotype 1 infection who fail to achieve an EVR at 12 weeks should be considered for cessation of treatment.
- Patients with genotype 1 infection with an EVR at 12 weeks should continue treatment for 48 weeks. Those who are still HCV RNA positive at 24 weeks should discontinue treatment.

B - Following informed discussion, treatment-naïve patients with genotype 1 infection and:

- Minimal or no fibrosis
- Low viral load (less than 400,000 IU/ml)
- Who achieve a rapid viral response (RVR) following a lead in with pegylated IFN and weight-based ribavirin for four weeks can be considered for 24 weeks of treatment without the addition of a protease inhibitor

Genotype 2 and 3 and Duration of Treatment

A - For patients with HCV genotype 2 or 3 standard treatment should be pegylated IFN and weight-based ribavirin for 24 weeks.

B - Non-cirrhotic patients, with genotype 2 or 3, who achieve an RVR at week 4 of therapy, could be considered for shortened duration of therapy of 12 to 16 weeks.

Genotype 4, 5 and 6 and Duration of Treatment

A - For patients with HCV genotype 4, 5 or 6 infection, standard treatment should be 48 weeks of pegylated IFN and weight-based ribavirin.

Patient Subgroups

Patients with Mild Chronic Hepatitis

B - Patients with mild CHC should be considered for treatment.

Patients with Persistently Normal ALT Levels

A - Patients with chronic hepatitis C and normal ALT should be considered for treatment.

Patients with HIV Co-Infection

A - All patients co-infected with HCV and HIV should be considered for HCV treatment.

A - For patients with HCV genotype 1 infection and HIV, who do not achieve an EVR, treatment should be stopped.

A -

- Co-infected non-genotype 1 patients who are considered suitable for treatment should be offered treatment with pegylated IFN and weight-based ribavirin for 48 weeks.
- Co-infected genotype 2 or 3 patients who achieve an RVR may be considered for 24 weeks of treatment.

C - All patients co-infected with HIV and HCV genotype 1 should be considered for treatment with a regimen which includes an HCV protease inhibitor.

B - Treatment-naive patients co-infected with HIV and HCV genotype 1 who are unsuitable for treatment with a regimen which includes HCV protease inhibitors should be considered for treatment with pegylated IFN and weight-based ribavirin for 48-72 weeks depending on viral response.

Patients with Hepatitis B Co-Infection

C - Patients with chronic hepatitis B and C co-infection should be considered for treatment with pegylated IFN and weight-based ribavirin.

Patients in Drug Treatment Programmes

B - Patients with CHC who are on a drug treatment programme should be considered for treatment.

Factors Influencing Effectiveness

Age, Gender and Ethnicity

A - Patients should be advised that older age at the time of treatment leads to a lower sustained viral response.

B - Patients should be advised about the likelihood of sustained viral response according to their ethnic origin.

Contraindications

Patients with Renal Failure

D - Patients with CHC and renal failure may be treated with IFN monotherapy, with careful monitoring required.

Patients with Mental Health Problems

B - Patients with stable mental health problems should not be excluded from treatment for CHC.

B - Patients with mental health problems should have their psychiatric symptoms monitored prior to and throughout IFN treatment.

Patients Taking Other Medicines

D - Patients should have a full drug history taken including prescribed, over-the-counter and illicit drugs.

D - The co-administration of any drugs should be assessed to ensure there is no unacceptable potential for toxicity or suboptimal efficacy of either agent.

Management of Adverse Effects

Flu-Like Symptoms

D - Patients experiencing flu-like side effects from pegylated IFN and ribavirin can be advised to use paracetamol within manufacturers' guidelines.

D - Patients should be advised to maintain an adequate fluid intake throughout treatment with pegylated IFN and ribavirin.

D - Patients should be advised to coordinate their injections of pegylated IFN and ribavirin with periods of reduced activity, such as weekends and holidays.

Anaemia and Neutropenia

B - Erythropoietin (EPO) should be considered in CHC patients receiving pegylated IFN and ribavirin therapy who develop anaemia, to prevent curtailment or dose reduction of ribavirin.

B - For patients receiving a protease inhibitor in combination with pegylated IFN and ribavirin therapy, consider ribavirin dose reduction as an alternative to the addition of EPO for controlling anaemia.

D - Granulocyte-colony stimulating factor should be considered on a case-by-case basis for patients who develop significant neutropenia while receiving treatment with pegylated IFN and ribavirin for CHC infection, to prevent curtailment or dose reduction of pegylated IFN.

Depression

B - All patients receiving pegylated IFN and ribavirin should be monitored for signs of depression before, during and immediately post-treatment.

B - Patients treated with pegylated IFN and ribavirin who experience depression should be considered for treatment with antidepressants and for referral to a specialist, if necessary.

Skin Reactions

D - All patients on pegylated IFN and ribavirin should be advised to ensure appropriate skin hygiene and hydration.

D - Patients should be advised to avoid overexposure to sun.

D - Patients should be advised to rotate injection sites.

D - The use of emollients and topical corticosteroids can be considered for non-specific rashes.

A - Patients taking telaprevir must be monitored closely for rash and treatment centres should have a rash management plan.

Thyroid Dysfunction

D - Thyroid function should be monitored at baseline before IFN therapy, at week 12 of treatment and at any time where there is a suspicion of thyroid dysfunction.

Dyspnoea

D - Patients treated with pegylated IFN or ribavirin who report dyspnoea that is not related to anaemia should be urgently assessed medically for cardiopulmonary problems.

Retinopathy

D - Patients with CHC and hypertension or diabetes should have an ophthalmic examination prior to commencing treatment, paying particular attention to cotton wool spots and retinal haemorrhage.

D - Any patient reporting visual disturbance during treatment should be examined further by an ophthalmologist.

D - IFN should be discontinued in any patient with visual disturbance until it has resolved or an ophthalmologist has confirmed there is no retinal injury.

Alopecia

D - Patients should be advised that treatment related hair loss is reversible on cessation of treatment.

Relapse or Failed Treatment

IFN and Ribavirin

D - Patients with CHC who have had unsuccessful treatment with non-pegylated IFN and ribavirin should be considered for pegylated IFN and ribavirin retreatment.

A - Patients with genotype 1 CHC who have had any unsuccessful treatment should be considered for treatment with a protease inhibitor based regimen.

Treatment of Advanced Infection

Antiviral Therapy

Patients with Cirrhosis

A - Patients with compensated cirrhosis should be considered for therapy, unless contraindicated.

A - Low-dose pegylated IFN maintenance monotherapy should not be used in patients with compensated cirrhosis.

Patients Referred for Liver Transplant

D - Patients in whom transplant is planned should not receive antiviral therapy in the pre-transplant or peri-transplant stages, except as part of clinical trials.

D - Patients should be considered for antiviral therapy post liver transplant to achieve HCV clearance in cases of recurrence of HCV related liver disease.

Liver Transplantation

C - Patients with hepatitis C virus and concurrent operable hepatocellular carcinoma should be offered liver transplantation.

C - Patients with HCV associated chronic liver failure should be considered for assessment for liver transplantation.

Screening for Hepatocellular Carcinoma (HCC)

A - The measurement of alfa-fetoprotein should not be used in isolation for screening or surveillance of the development of HCC in patients with hepatitis C.

D - Surveillance using ultrasound should take place at six-monthly intervals.

C - Surveillance should be confined to patients with cirrhosis.

Nutrition, Supportive Care and Complementary Therapies

Nutritional Interventions

Dietary Interventions

D -

- Nutritional care for people infected with hepatitis C should involve promotion of optimal nutrition and prevention or treatment of malnutrition or deficiencies of specific nutrients.
- Patients should have a nutritional screen and if needed a nutritional assessment and appropriate advice from a dietitian.

D - Patients with advanced liver disease should be given nutritional support to minimise malnutrition.

Overweight

C - Patients who are overweight should be advised to lose weight, within a realistic weight loss target, as this may have a beneficial effect on the degree of liver damage associated with hepatitis C infection.

Exercise

D - Patients with hepatitis C should be encouraged to take mild to moderate exercise. Those on antiviral therapy should be advised that they may find their capacity for exercise reduced.

Definitions:

Levels of Evidence

1++: High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+: Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

1-: Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++: High quality systematic reviews of case control or cohort studies

High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+: Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2-: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3: Non-analytic studies (e.g., case reports, case series)

4: Expert opinion

Grades of Recommendation

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A: At least one meta-analysis, systematic review of RCTs rated as 1++ and directly applicable to the target population; *or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D: Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Clinical Algorithm(s)

The following clinical algorithms are provided in the original guideline document:

- Algorithm for the use of protease inhibitors in treatment-naive HCV genotype 1 infected patients
- Algorithm for the use of protease inhibitors in HCV genotype 1 infected patients who have had prior virological failure on treatment

Scope

Disease/Condition(s)

Hepatitis C virus (HCV) infection

Other Disease/Condition(s) Addressed

- Hepatitis A
- Hepatitis B
- Human Immunodeficiency Virus (HIV)

Guideline Category

Diagnosis

Evaluation

Management

Prevention

Risk Assessment

Screening

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Internal Medicine

Obstetrics and Gynecology

Pediatrics

Surgery

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide evidence based recommendations covering all stages of the patient care pathway: screening, testing, diagnosis, referral, treatment, care and follow up of infants, children and adults with, or exposed to, hepatitis C virus (HCV) infection

Target Population

Infants, children and adults with, or exposed to, hepatitis C virus (HCV) infection

Interventions and Practices Considered

Diagnosis/Evaluation

1. Dried blood spot testing
2. Hepatitis C virus (HCV) genotyping
3. HCV antibody testing
4. HCV ribonucleic acid (RNA) testing
5. Assessment of liver disease:
    - Biochemical tests
    - Liver biopsy
6. Assessment for risk factors for progression of untreated disease (e.g., age, gender, ethnicity; smoking; alcohol use; human immunodeficiency virus [HIV] or hepatitis A or B co-infection)
7. Screening for hepatocellular carcinoma (HCC)

Prevention/Management/Treatment

1. Secondary prevention:
    - Safe sex and use of condoms
    - Avoidance of percutaneous or mucous membrane exposure (e.g., sharing of razors, toothbrushes)
    - Advising drug users how to prevent transmission to others
    - Avoidance of exposure prone procedures for healthcare professionals that are HCV RNA positive
2. Multidisciplinary care
3. Referral to specialist care
4. Monitoring of HCV-infected children to identify risk of fibrosis and determine treatment
5. Treatment in children: pegylated interferon (IFN) and ribavirin
6. Treatment of acute HCV: pegylated or non-pegylated IFN
7. Treatment of chronic HCV: pegylated IFN and weight-based ribavirin ± protease inhibitor
8. Consideration of factors that affect treatment effectiveness
9. Management of adverse effects of treatment

10. Liver transplant
11. Nutritional screening and assessment
12. Encouraging weight loss and exercise

Major Outcomes Considered

- Acute hepatitis C symptoms
- Chronic infection
- Mortality
- Adverse effects
- Quality of life
- Sustained viral response

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Systematic Literature Review

The evidence base for this guideline was synthesised in accordance with Scottish Intercollegiate Guidelines Network (SIGN) methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, EMBASE, CINAHL, PsycINFO, and the Cochrane Library. The year range covered was 2006-2012. Internet searches were carried out on various websites including the US National Guideline Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by one member of the group and one SIGN staff member using standard SIGN methodological checklists before conclusions were considered as evidence.

Literature Search for Patient Issues

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to early management of patients with hepatitis C. Databases searched include Medline, EMBASE, CINAHL, and PsycINFO, and the results were summarised and presented to the guideline development group.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

1++: High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+: Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

1-: Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++: High quality systematic reviews of case control or cohort studies

High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+: Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2-: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3: Non-analytic studies (e.g., case reports, case series)

4: Expert opinion

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Once papers have been selected as potential sources of evidence, the methodology used in each study is assessed to ensure its validity. The result of this assessment will affect the level of evidence allocated to the paper, which will in turn influence the grade of recommendation that it supports.

The methodological assessment is based on a number of key questions that focus on those aspects of the study design that research has shown to have a significant influence on the validity of the results reported and conclusions drawn. These key questions differ between study types, and a range of checklists is used to bring a degree of consistency to the assessment process. The Scottish Intercollegiate Guidelines Network (SIGN) has based its assessments on the MERGE (Method for Evaluating Research and Guideline Evidence) checklists developed by the New South Wales Department of Health, which have been subjected to wide consultation and evaluation. These checklists were subjected to detailed evaluation and adaptation to meet SIGN's requirements for a balance between methodological rigour and practicality of use.

The assessment process inevitably involves a degree of subjective judgement. The extent to which a study meets a particular criterion (e.g., an acceptable level of loss to follow up) and, more importantly, the likely impact of this on the reported results from the study will depend on the clinical context. To minimise any potential bias resulting from this, each study must be evaluated independently by at least two group members. Any differences in assessment should then be discussed by the full group. Where differences cannot be resolved, an independent reviewer or an experienced member of SIGN executive staff will arbitrate to reach an agreed quality assessment.

Evidence Tables

Evidence tables are compiled by SIGN executive staff based on the quality assessments of individual studies provided by guideline development group members. The tables summarise all the validated studies identified from the systematic literature review relating to each key question. They are presented in a standard format to make it easier to compare results across studies, and will present separately the evidence for each outcome measure used in the published studies. These evidence tables form an essential part of the guideline development record and ensure that the basis of the guideline development group's recommendations is transparent.

Additional details can be found in the companion document titled "SIGN 50: A Guideline Developers' Handbook." (Edinburgh [Scotland]: Scottish Intercollegiate Guidelines Network. [SIGN publication; no. 50]), available from the SIGN Web site .

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Synthesising the Evidence

Guideline recommendations are graded to differentiate between those based on strong evidence and those based on weak evidence. This

judgement is made on the basis of an (objective) assessment of the design and quality of each study and a (perhaps more subjective) judgement on the consistency, clinical relevance and external validity of the whole body of evidence. The aim is to produce a recommendation that is evidence-based, but which is relevant to the way in which health care is delivered in Scotland and is therefore implementable.

It is important to emphasise that the grading does not relate to the importance of the recommendation, but to the strength of the supporting evidence and, in particular, to the predictive power of the study designs from which that data was obtained. Thus, the grading assigned to a recommendation indicates to users the likelihood that, if that recommendation is implemented, the predicted outcome will be achieved.

Considered Judgement

It is rare for the evidence to show clearly and unambiguously what course of action should be recommended for any given question. Consequently, it is not always clear to those who were not involved in the decision making process how guideline developers were able to arrive at their recommendations, given the evidence they had to base them on. In order to address this problem, SIGN has introduced the concept of considered judgement.

Each guideline group considers the following factors:

- Quantity, quality, and consistency of evidence
- External validity (generalisability) of studies
- Directness of application to the target population for the guideline
- Any evidence of potential harms associated with implementation of a recommendation
- Clinical impact (i.e., the extent of the impact on the target patient population, and the resources needed to treat them in accordance with the recommendation)
- Whether, and to what extent, any equality groups may be particularly advantaged or disadvantaged by the recommendations made
- Implementability (i.e., how practical it would be for the National Health Service (NHS) Scotland to implement the recommendation)

Then the group is asked to summarise its view on all of these issues, both the quality of the evidence and its potential impact, before making a graded recommendation. This summary should be succinct, and taken together with its views of the level of evidence represent the first draft of the text that will appear in the guideline immediately before a graded recommendation.

Additional detail about SIGN's process for formulating guideline recommendations is provided in Section 7 of the companion document titled "SIGN 50: A Guideline Developers' Handbook." (Edinburgh [Scotland]: Scottish Intercollegiate Guidelines Network. [SIGN publication; no. 50], available from the SIGN Web site .

Rating Scheme for the Strength of the Recommendations

Grades of Recommendation

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A: At least one meta-analysis, systematic review of randomised controlled trial (RCT) rated as 1++, and directly applicable to the target population; *or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D: Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Cost Analysis

Clinical and Cost-Effective Testing for Hepatitis C Virus (HCV)

Controlled trials or cohort studies to gauge the cost effectiveness of offering an HCV test to different population groups have not been undertaken. Limited evidence from economic modeling work, indicates that offering an HCV test to former injecting drug users (IDU) in drug treatment and perhaps other settings would convey cost-effective clinical benefits. Former IDU are more likely to have a higher prevalence of HCV and comply with therapy than current IDU. Models of best practice for the identification and testing of former IDU have not been developed and evaluated. Expert opinion suggests that general practices, particularly those that serve areas with a high prevalence of drug use, may constitute environments where focused, well supported testing initiatives might be successful. Prisons may also offer similar opportunities. Targeted and generalised HCV awareness/testing campaigns have been conducted but no evaluations of their success in encouraging people (including former IDU) at high risk of HCV to engage with services have been reported.

In populations where the prevalence of HCV is low (e.g., genitourinary medicine clinic attendees), economic modelling indicates that universal testing does not convey cost-effective clinical benefit.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The national open meeting is the main consultative phase of Scottish Intercollegiate Guidelines Network (SIGN) guideline development.

Peer Review

All SIGN guidelines are reviewed in draft form by independent expert referees, who are asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. A number of general practitioners (GPs) and other primary care practitioners also provide comments on the guideline from the primary care perspective, concentrating particularly on the clarity of the recommendations and their assessment of the usefulness of the guideline as a working tool for the primary care team. The draft is also sent to at least two lay reviewers in order to obtain comments from the patient's perspective.

It should be noted that all reviewers are invited to comment as individuals, not as representatives of any particular organisation or group. Corporate interests, whether commercial, professional, or societal have an opportunity to make representations at the national meeting stage where they can send representatives to the meeting or provide comment on the draft produced for that meeting. Peer reviewers are asked to complete a declaration of interests form.

The comments received from peer reviewers and others are carefully tabulated and discussed with the Chair and with the Guideline Development Group (GDG). Each point must be addressed and any changes to the guideline as a result noted or, if no change is made, the reasons for this recorded.

As a final quality control check prior to publication, the guideline and the summary of peer reviewers' comments are reviewed by the SIGN Editorial Group for that guideline to ensure that each point has been addressed adequately and that any risk of bias in the GDG process as a whole has been minimised. Each member of the guideline development group is then asked formally to approve the final guideline for publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management of patients with or exposed to hepatitis C virus (HCV)

Potential Harms

- Adverse effects of interferon (IFN) and ribavirin therapy include (see Section 10.6, "Management of Adverse Effects," in the original guideline document) for more information:
  - Flu-like symptoms
  - Anaemia and neutropenia
  - Depression
  - Skin reactions
  - Thyroid dysfunction
  - Weight loss
  - Dyspnoea
  - Retinopathy
  - Alopecia
  - Other side effects (insomnia, poor concentration, oral disease, anal/rectal discomfort, gastrointestinal problems, altered taste, nausea, fatigue, and post-treatment withdrawal symptoms)
- Patients with mental health problems should have their psychiatric symptoms monitored prior to and throughout IFN treatment.
- The co-administration of any drugs should be assessed to ensure there is no unacceptable potential for toxicity or suboptimal efficacy of either agent.
- Patients should be made aware of potentially dangerous interactions between over-the-counter medicines, illicit drugs and hepatitis C virus (HCV) therapy, even if they are not known to use illicit drugs.

Contraindications

Contraindications

Pregnancy and Risk of Pregnancy

- Pegylated interferon (IFN) and ribavirin must not be prescribed to women who are pregnant.
- Treatment with pegylated IFN and ribavirin should not be initiated until pregnancy has been excluded.
- Couples, with one partner receiving pegylated IFN and ribavirin, should use two forms of contraception during treatment and for six months after therapy has ended.

Qualifying Statements

Qualifying Statements

- This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is, however, advised that significant departures from the national guideline or any local guidelines derived from it should be fully

documented in the patient's case notes at the time the relevant decision is taken.

- The remit encompasses prevention of secondary transmission of the virus but specifically excludes primary prevention of hepatitis C virus (HCV) infection. Primary prevention of hepatitis C infection is an important public health concern but is outwith the remit of this guideline. The principles and evidence for the prevention of blood borne viruses are generalisable and while reviewing this large body of evidence would have been beyond the capacity of the guideline development group, reviewing the HCV evidence alone would have produced a distorted view.
- Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.
  Medicines may be prescribed off label in the following circumstances:

  - For an indication not specified within the marketing authorisation
  - For administration via a different route
  - For administration of a different dose
  - For a different patient population

  An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

  Generally the off label use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.

  "Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability."

  The General Medical Council (GMC) recommends that when prescribing a medicine off-label, doctors should:

  - Be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
  - Be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
  - Record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
  - Take responsibility for prescribing the medicine and for overseeing the patient's care, including the monitoring the effects of the medicine

  Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

  Prior to any prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.

Implementation of the Guideline

Description of Implementation Strategy

Implementation of national clinical guidelines is the responsibility of each National Health Service (NHS) Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Mobile Device Resources

Patient Resources

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Scottish Intercollegiate Guidelines Network (SIGN). Management of hepatitis C. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2013 Jul. 57 p. (SIGN publication; no. 133). [232 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

Scottish Intercollegiate Guidelines Network - National Government Agency [Non-U.S.]

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Scottish Executive Health Department

Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Declarations of interests were made by all members of the guideline development group. Further details are available from the Scottish Intercollegiate Guidelines Network (SIGN) Executive.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Scottish Intercollegiate Guidelines Network (SIGN). Management of hepatitis C. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2006 Dec. 49 p. (SIGN publication; no. 92).

Any amendments to the guideline in the interim period will be noted on Scottish Intercollegiate Guidelines Network (SIGN) Web site .

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Scottish Intercollegiate Guidelines Network (SIGN) Web site .

Availability of Companion Documents

The following are available:

- Quick reference guide: Management of hepatitis C. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network; 2013 Jul. 2 p. Electronic copies: Available in Portable Document Format (PDF) from the Scottish Intercollegiate Guidelines Network (SIGN) Web site .
- SIGN 50: A guideline developer's handbook. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network. (SIGN publication; no. 50). Electronic copies: Available from the SIGN Web site .

In addition, Section 14 of the original guideline document contains key points to audit.

Executive summaries of SIGN guidelines are available for mobile devices through the guidelines app on the SIGN Web site .

Patient Resources

The following is available:

- Information about hepatitis C for patients and carers. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network; 2013. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Scottish Intercollegiate Guidelines Network (SIGN) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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